PASS INFORMATION

Title	Aclidinium Bromide Post-Authorisation Safety Study to Evaluate the Risk of Cardiovascular Endpoints: Arrhythmias
Version identifier of the final study report	1.0
Date of last version of the final study report	17 November 2023
EU PAS Register number	EUPAS13616
Active substance	Aclidinium bromide (ATC code: R03BB05) Aclidinium bromide/formoterol fumarate dihydrate (ATC code: R03AL05)
Medicinal product	Eklira® Genuair®/Bretaris® Genuair® Duaklir® Genuair®/Brimica® Genuair®
Product reference	Eklira® Genuair®: H0002211 Bretaris® Genuair®: H0002706 Duaklir® Genuair®: H0003745 Brimica® Genuair®: H0003969
Procedure number	Eklira® Genuair®: EMEA/H/C/002211 Bretaris® Genuair®: EMEA/H/C/002706 Duaklir® Genuair®: EMEA/H/C/003745 Brimica® Genuair®: EMEA/H/C/003969
Marketing authorisation holder(s)	Covis Pharma Europe B.V.
Joint PASS	No
Research question and objectives	The overall objective of the aclidinium post-authorisation safety study (PASS) is to evaluate the potential cardiovascular safety concerns and all-cause mortality described in the risk management plan for aclidinium bromide through sequential cohort substudies for each endpoint of interest. The objectives of the arrhythmias component of the PASS are as follows: (1) To compare the risk of arrhythmias (including any cardiac arrhythmia, atrial fibrillation, and serious ventricular arrhythmia) in patients with chronic obstructive pulmonary disease (COPD) initiating treatment with aclidinium/formoterol and other selected COPD medications (each study cohort) with the risk of

	arrhythmias in patients with COPD initiating treatment with long-acting beta2-agonists (LABAs) (2) To compare the risk of arrhythmias in patients with COPD initiating treatment with COPD treatments (each study cohort) with the risk of arrhythmias in patients initiating treatment with aclidinium/formoterol and aclidinium (3) To evaluate the effect of duration of use of each study medication on the risk of arrhythmias
Country(-ies) of study	United Kingdom: the Clinical Practice Research Datalink (CPRD)
Author	Cristina Rebordosa, MD, PhD, RTI Health Solutions [redacted], RTI Health Solutions

MARKETING AUTHORISATION HOLDER(S)

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RTI Health Solutions has obtained from the CPRD a waiver for the masking of cells with non-zero but less than 5 events for regulatory submission reports (29 October 2018)

This version of the report cannot be disseminated beyond the regulatory reviewers. Small cell counts need to be suppressed if the regulators wish to publish or disseminate this report in the interest of transparency. All cell counts from 1 to 4 in this report have been highlighted clearly with a note that these would have to be redacted if shared outside the regulatory environment.

During the conduct of the study, the marketing authorisation holder of aclidinium (Eklira) and aclidinium/formoterol (Duaklir) changed from AstraZeneca to Covis Pharma. Therefore, starting 01 January 2023, the research team at RTI Health Solutions was no longer authorised to use the CPRD data extracted and processed for this study and was required to destroy the raw data obtained under AstraZeneca's licence.

At the time of the MAH switch, the analyses for this study had been completed, except for the sensitivity analysis extending the carryover period from 7 to 30 days, which could not be performed (see additional details in Section 8).

APPROVAL PAGE: RTI HEALTH SOLUTIONS

Project Title: Aclidinium Bromide Post-Authorisation Safety Study to Evaluate the Risk of Cardiovascular Endpoints: Arrhythmias

Document type: Study Report

Version: 1.0

RTI-HS Project No.: 0306182

Authors: Cristina Rebordosa, MD, PhD; [redacted]
(RTI Health Solutions)

Please sign below to acknowledge that you have read and approve of this document:

[redacted] 22-Nov-2023

Cristina Rebordosa, MD, PhD
Senior Director of Epidemiology, RTI Health Solutions

Date

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APPROVAL PAGE: COVIS PHARMA

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22-Nov-2023

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Pharmacovigilance

Date

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1 Abstract

Title: Aclidinium Bromide Post-Authorisation Safety Study to Evaluate the Risk of Cardiovascular Endpoints: Arrhythmias

Version: 1.0, 17 November 2023

Authors: Cristina Rebordosa, MD, PhD, and [redacted]

Keywords: aclidinium/formoterol; aclidinium bromide; LAMA; chronic obstructive pulmonary disease; arrhythmias; database study

Rationale and background: Aclidinium bromide is an inhaled long-acting anticholinergic (LAMA) approved in Europe in 2012 as maintenance bronchodilator treatment to relieve symptoms in adults with chronic obstructive pulmonary disease (COPD).

A series of substudies were planned to evaluate potential cardiovascular safety concerns identified in the aclidinium risk management plan in order to address cardiovascular concerns associated with LAMA use. The previous substudies did not observe an increased risk of all-cause mortality, congestive heart failure, myocardial infarction, or stroke associated with the use of aclidinium. The present substudy report describes the results of evaluation of the arrhythmias endpoint for the aclidinium in fixed-dose combination (FDC) with formoterol, conducted in the Clinical Practice Research Datalink (CPRD) in the United Kingdom (UK).

Research question and objectives: (1) To compare the risk of arrhythmias (including any cardiac arrhythmia, atrial fibrillation, and serious ventricular arrhythmia) in patients with COPD initiating treatment with aclidinium/formoterol and other selected COPD medications (each study cohort) with the risk of arrhythmias in patients with COPD initiating treatment with long-acting beta2-agonists (LABAs). (2) To compare the risk of arrhythmias in patients with COPD initiating treatment with COPD treatments (i.e., LABA, tiotropium, other LAMA, LAMA/LABA, LABA/ICS, and LAMA/LABA/ICS) with the risk of arrhythmias in patients initiating treatment with aclidinium/formoterol and aclidinium. (3) To evaluate the effect of duration of use of each study medication on the risk of arrhythmias.

Study design: Non-interventional database cohort study of patients with COPD aged 40 years or older starting (new users) treatment with aclidinium, aclidinium/formoterol, tiotropium, other LAMA (glycopyrronium or umeclidinium), LAMA/LABA, LABA/inhaled corticosteroids (LABA/ICS), LABA, or LAMA/LABA/ICS.

Setting: The primary care Aurum database of the CPRD in the UK, from January 2015 through March 2021. The study included all practices where linkage was available to obtain information on date and cause of death from the Office for National Statistics (ONS) and information on hospitalisations from the Hospital Episode Statistics (HES) database.

Subjects and study size, including dropouts: A total of 11,393 new users of aclidinium and 7,816 new users of aclidinium/formoterol were identified. The percentage of eligible patients included after applying both inclusion and exclusion criteria was 40.8% among users of aclidinium and 50.8% among users of aclidinium/formoterol.

Variables and data sources: Exposure to the study medications was ascertained through prescription information recorded in the CPRD. The endpoint of any cardiac arrhythmia was defined as any cardiac arrhythmia event that was the primary reason for hospitalisation or an underlying cause of death. Atrial fibrillation and serious ventricular arrythmia are two separate endpoints that were derived similarly. Serious ventricular arrythmia included torsade de pointes, ventricular tachycardia, and ventricular fibrillation or flutter. The main risk factors evaluated included age, sex, smoking, body mass index (BMI), COPD severity, comorbidity, comedications, and utilisation of health care resources. Crude incidence rates for any cardiac arrhythmia, atrial fibrillation, and severe ventricular arrhythmia were estimated for current use of each study medication. Crude and adjusted incidence rate ratios (IRRs) were estimated for current, recent, and past use of each study medication versus current use of LABA. Risks were estimated for current single use and current multiple use and by duration of current use of the study medications. Several subgroup and sensitivity analyses were also conducted.

Results: The study included 11,393 new users of aclidinium, 7,816 new users of aclidinium/formoterol, 57,106 new users of tiotropium, 30,637 new users of other LAMA, 31,912 new users of LAMA/LABA, 75,082 new users of LABA/ICS, 32,394 new users of LAMA/LABA/ICS, and 12,070 new users of LABA. The distributions of age, sex, race, current smoking, BMI, alcohol abuse, and deprivation index were similar across the study medications. LAMA/LABA/ICS new users had more severe COPD (43.5% in Category D) than new users of the other study medications (ranging from 15.4% for LABA to 29.2% for aclidinium). Having a recorded diagnosis of asthma in the 5 years before the start date was more frequent among new users of LABA/ICS (51.0%). Overall, LAMA/LABA/ICS users appeared to have more comorbidities (e.g., pneumonia) than users of other study medications. Aclidinium bromide and LAMA/LABA/ICS users had the highest frequency of general practitioner (GP) visits (i.e., 26 or more GP visits) within the 12 months before the start date.

Crude incidence rates per 1,000 person-years for any cardiac arrhythmias, during current use, ranged from 3.98 for LAMA/LABA to 7.44 for aclidinium/formoterol. The crude incidence rates for atrial fibrillation, during current use, ranged from 2.73 for LAMA/LABA to 5.37 for aclidinium/formoterol. Crude incidence rates per 1,000 person-years for serious ventricular arrhythmia, during current use, were less than 0.5 for all study medications, with wide 95% confidence intervals (CIs). Current users of aclidinium/formoterol had an adjusted IRR (95% CI) of 1.76 (1.19-2.62) for any cardiac arrhythmia and 1.73 (1.08-2.78) for atrial fibrillation when compared with current use of LABA. (Abstract Table 1).

Abstract Table 1. Risk of arrhythmias associated with current use of the study medications versus current use of LABA

Current use	Number of events	Person-years	Crude incidence rate per 1,000 PY (95% CI)	Crude incidence rate ratio (95% CI)	Adjusted[a] incidence rate ratio (95% CI)
Any cardiac arrhythmias					
LABA	53	11,543	4.59 (3.44, 6.01)	1.0 (REF)	1.0 (REF)
Aclidinium	77	14,421	5.34 (4.21, 6.67)	1.16 (0.82, 1.65)	1.07 (0.75, 1.54)
Aclidinium/formoterol	65	8,739	7.44 (5.74, 9.48)	1.62 (1.13, 2.33)	1.76 (1.19, 2.62)
Tiotropium	413	77,576	5.32 (4.82, 5.86)	1.16 (0.87, 1.54)	1.16 (0.87, 1.54)
Other LAMA	183	39,684	4.61 (3.97, 5.33)	1.00 (0.74, 1.36)	1.06 (0.77, 1.46)
LAMA/LABA	153	38,471	3.98 (3.37, 4.66)	0.87 (0.63, 1.18)	0.90 (0.64, 1.28)
LABA/ICS	610	119875	5.09 (4.69, 5.51)	1.11 (0.84, 1.47)	1.19 (0.90, 1.58)
LAMA/LABA/ICS	147	33,782	4.35 (3.68, 5.11)	0.95 (0.69, 1.30)	1.52 (0.77, 3.02)
Atrial fibrillation					
LABA	43	11,552	3.72 (2.69, 5.01)	1.0 (REF)	1.0 (REF)
Aclidinium	64	14,434	4.43 (3.41, 5.66)	1.19 (0.81, 1.75)	1.17 (0.78, 1.75)
Aclidinium/formoterol	47	8,752	5.37 (3.95, 7.14)	1.44 (0.95, 2.18)	1.73 (1.08, 2.78)
Tiotropium	303	77,696	3.90 (3.47, 4.36)	1.05 (0.76, 1.44)	1.07 (0.77, 1.47)
Other LAMA	139	39,716	3.50 (2.94, 4.13)	0.94 (0.67, 1.32)	1.02 (0.71, 1.47)
LAMA/LABA	105	38,500	2.73 (2.23, 3.30)	0.73 (0.51, 1.04)	0.79 (0.53, 1.18)
LABA/ICS	468	120049	3.90 (3.55, 4.27)	1.05 (0.77, 1.43)	1.11 (0.81, 1.52)
LAMA/LABA/ICS	105	33,811	3.11 (2.54, 3.76)	0.83 (0.59, 1.19)	1.55 (0.66, 3.63)
Serious ventricular arrhythmia					
LABA	5	11,610	0.43 (0.14, 1.01)	1.0 (REF)	1.0 (REF)
Aclidinium	[redacted]	[redacted]	0.14 (0.02, 0.50)	0.32 (0.06, 1.65)	0.25 (0.05, 1.32)
Aclidinium/formoterol	[redacted]	[redacted]	0.45 (0.12, 1.16)	1.06 (0.28, 3.93)	0.91 (0.24, 3.43)
Tiotropium	17	78,014	0.22 (0.13, 0.35)	0.51 (0.19, 1.37)	0.48 (0.17, 1.30)
Other LAMA	10	39,858	0.25 (0.12, 0.46)	0.58 (0.20, 1.70)	0.58 (0.20, 1.72)
LAMA/LABA	[redacted]	[redacted]	0.05 (0.01, 0.19)	0.12 (0.02, 0.62)	0.11 (0.02, 0.57)
LABA/ICS	23	120652	0.19 (0.12, 0.29)	0.44 (0.17, 1.16)	0.47 (0.18, 1.25)
LAMA/LABA/ICS	8	33,877	0.24 (0.10, 0.47)	0.55 (0.18, 1.68)	0.59 (0.18, 1.95)

CI = confidence interval; ICS = inhaled corticosteroid; LABA = long-acting beta2-agonist; LAMA = long-acting anticholinergic; PY = person-years; REF = reference category.

Note: The number of events and person-years for current use of LABA (reference category) differed across the study medications. Current users of both LABA and the specific study medication of interest were excluded from each corresponding analysis.

Note: Per the CPRD small cell count policy, cells counts with n between 1 and 4, and any additional cells that may lead to calculation of a cell count of 1 to 4, need to be suppressed if the regulators wish to publish this information in the interest of transparency. Therefore, in this table, the value has to be reported as "n < 5."

[a] For any cardiac arrhythmia, the models were adjusted by age, sex, COPD severity, and calendar year. For atrial fibrillation, the models were adjusted by age, sex, COPD severity, calendar year, number of prescriptions for respiratory medications, and prior use of aclidinium. For serious ventricular arrhythmia, the models were adjusted by age, sex, and COPD severity.

Compared with current single use of LABA, current single use of aclidinium and current single and multiple use of aclidinium/formoterol had a higher adjusted IRR for any cardiac arrhythmia. A similar pattern was shown for atrial fibrillation. For aclidinium bromide, the adjusted IRR for any cardiac arrhythmia was 1.68 (95% CI, 1.02-2.75) for current single use and 1.09 (95% CI, 0.64-1.86) for current multiple use. For aclidinium/formoterol, the adjusted IRR for any cardiac arrhythmia was 2.00 (95% CI, 1.22-3.27) for current single use and 2.71 (95% CI, 1.26-5.80) for current multiple use. For aclidinium, the adjusted IRR for atrial fibrillation was 1.77 (95% CI, 1.02-3.05) for current single use and 1.23 (95% CI, 0.64-2.36) for current multiple use. For aclidinium/formoterol, the adjusted IRR for atrial fibrillation was 2.07 (95% CI, 1.15-3.72) for current single use and 2.51 (95% CI, 0.97-6.50) for current multiple use. For aclidinium bromide, the adjusted IRR for serious ventricular arrhythmia was 0.35 (95% CI, 0.04-3.42) for current single use and 0.16 (95% CI, 0.02-1.73) for current multiple use. For aclidinium/formoterol, the adjusted IRR for serious ventricular arrhythmia was 0.96 (95% CI, 0.21-4.31) for current single use and non-evaluable for current multiple use.

When compared with aclidinium bromide, an increased risk of any cardiac arrhythmia was observed for current use of aclidinium/formoterol. The adjusted IRRs was 1.44 (95% CI, 1.01-2.05). When compared with aclidinium/formoterol, a decreased risk of any cardiac arrhythmia was observed for current use of each study medication. Additionally, a decreased risk of atrial fibrillation was observed for tiotropium, other LAMA, and LAMA/LABA. A decreased risk of serious ventricular arrhythmia was observed for LAMA/LABA. The adjusted IRRs ranged from 0.53 (0.40, 0.72) to 0.73 (95% CI, 0.56-0.95) for any cardiac arrhythmia, from 0.49 (95% CI, 0.34-0.71) to 0.76 (95% CI, 0.50-1.15) for atrial fibrillation, and from 0.11 (95% CI, 0.02-0.62) to 1.09 (95% CI, 0.29-4.10) for serious ventricular arrhythmia when compared with current use of aclidinium/formoterol.

No meaningful increased risk of any cardiac arrhythmia, atrial fibrillation, or serious ventricular arrhythmia was observed for short or long duration of current use of any of the study medications compared with current short or long use of LABA, respectively, except for long duration of use of aclidinium/formoterol versus long duration of use of LABA, which showed an adjusted IRR for any cardiac arrhythmia of 1.64 (95% CI, 1.02-2.64) and an adjusted IRR for atrial fibrillation of 2.09 (95% CI, 1.19-3.69). For serious ventricular arrhythmia, precision of effect estimates was low, as it was based on a very low number of events.

Most of the subgroup analyses were not evaluable for the serious ventricular arrythmia outcome. Overall, the results across categories of COPD severity, age, and history of asthma were similar to those observed in the main analysis. For any cardiac arrhythmia and atrial fibrillation, all the

study medications were compared with use of LABA; the IRR estimates were generally lower for patients in GOLD 2016 COPD severity category D than for those in category B. However, incidence rate estimates were higher for those in category D than for those in category B. IRR estimates were higher for patients without asthma than for patients with asthma. For any cardiac arrhythmia, IRR estimates were generally lower during the COVID-19 pandemic than before the COVID-19 era. A sensitivity analysis was conducted adding secondary discharge diagnoses in HES to the definition of study outcomes. Compared with the main analysis, which was based on primary discharge diagnoses only, the number of events increased for all study medications. The IRRs for any cardiac arrhythmia and atrial fibrillation were similar to those obtained in the main analysis, except for aclidinium/formoterol users, for whom the IRRs were below 1 and the 95% CI included 1. For serious ventricular arrythmia, the IRR of aclidinium/formoterol users also differed from the main analysis: the IRR was above 1, and the 95% CI included 1.

Discussion: Overall, results from this study indicate that the current use of aclidinium/formoterol and LAMA/LABA/ICS showed an increased risk of any cardiac arrhythmia and atrial fibrillation compared with current use of LABA. Similarly, current use of aclidinium/formoterol and LAMA/LABA/ICS showed an increased risk of any cardiac arrhythmia and atrial fibrillation when compared with current use of aclidinium.

Results from the sensitivity analysis using propensity scores suggest that differences could be partially explained by some degree of confounding. The potential for time varying confounding and immortal bias in the results for long duration of use suggests that results for short duration of use may be closer to the true effect of the exposure to aclidinium and aclidinium/formoterol on the risk of the outcomes of interest. While no increased risk of serious ventricular arrhythmia was observed, as described in the study protocol, the study size was limited for the assessment of this outcome. No increased risk of any cardiac arrhythmia, atrial fibrillation, or serious ventricular arrhythmia was observed among users of aclidinium compared with users of LABA.

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